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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,923	SAVIO ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17,20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17, 20, 22, and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/2007 has been entered.

2. In the response received on 8/8/2007, the Applicants cancelled claims 18-19 and 21, and added new claim 23. Therefore, claims 14-17, 20, and 22-23 are currently pending and are the subject of this office action.

Claim Objections

1. Objections to claims 16-17 and 20, as set forth on page 2 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicants' amendments to the claims to recite "wherein the method comprises".

2. Objection to claim 22, as set forth on page 2 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicant's amendments to the claim to recite "autologous IL-15, wherein said method comprises".

3. Objection to claim 15 for failing to further limit the subject matter of a previous claim, as set forth on pages 2-3 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicants' amending claim 15 to be in independent form, rather than dependent from claim 14.

4. The Examiner suggests amending claim 16 to recite "wherein the expression-related disease". Furthermore, the claim recites the general term "autoimmune disease", followed by specific autoimmune

diseases "rheumatoid arthritis, psoriasis, multiple sclerosis, etc). It is suggested that Applicants separate the specific autoimmune diseases into a separate, dependent claim.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejections maintained

1. Claims 16-17, and 20 *remain rejected*, under 35 USC § 112, first paragraph, regarding lack of enablement for methods of treating disorders associated with expression of IL-15, wherein said methods comprise administration of a composition comprising human IL-15 as an antigen for generating neutralizing antibodies in humans, as set forth on pages 3-4 of the office action mailed on 4/4/2007 and pages 4-5 of the office action mailed on 9/12/2006.

The claims of the instant invention are drawn to methods for treating "IL-15 expression-related diseases" in a patient, wherein said method comprises administering a composition of IL-15 and aluminum hydroxide. The claims recite IL-15 expression related diseases including autoimmune disease, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, and leukemia. In the response received on 8/8/2007, the Applicants argue that the claims have been amended to recite specific IL-15 expression-related diseases, and therefore the rejection over treatment of "any IL-15 expression related disease" is overcome.

This argument has been fully considered and is not persuasive. As written, the breadth of claim 16 is still excessive because it reads on treatment of all possible types of autoimmune disease in addition to the specific diseases subsequently recited. Although the specification teaches that IL-15 expression is associated with several autoimmune diseases such as rheumatoid arthritis and Crohn's disease, there is no disclosure of IL-15 expression with all other types of autoimmune disease, such as myasthenia gravis, Graves' disease, or pernicious anemia, which have not been disclosed as being associated with increased IL-15 expression. Thus, the specification is not enabling for the full breadth of claim 16.

Furthermore, the instant specification provides guidance and working examples showing that a composition comprising human IL-15 and Freund's adjuvant is capable of generating anti-IL-15 neutralizing antibodies in monkeys. Even if one assumes that this composition, or one comprising human IL-15 and the adjuvant aluminum hydroxide, can generate neutralizing anti-IL-15, the specification does

not provide guidance and examples showing treatment of any disease. Although one of skill in the art would know that increased IL-15 expression is associated with several of the claimed diseases, a skilled artisan would not necessarily predict that these diseases could be effectively treated simply by neutralization of IL-15. For example, Al-Mughales *et al* (*Clin. Exp. Immunol.*, 1996, Vol 106, pages 230-236) shows that rheumatoid arthritis is characterized by increased expression in synovial fluid of numerous cytokines, such as IL-15, IL-8, monocytes chemotactic protein-1, and macrophage inflammatory protein-1α (see abstract, Table 2). However, neutralization of any single cytokine did not abolish activity of synovial fluid, and combinations of neutralizing antibodies were required to inhibit synovial fluid activity (see abstract, Figure 4). Specifically, anti-IL-15 antibodies alone were ineffective in abolishing activity in a lymphocyte polarization assay (see Figure 4).

Obermeier *et al* (*Eur. J. Immunol.*, 2006, Vol 36, p. 2691-2699) teaches that IL-15 expression in inflammatory bowel disease may be protective, rather than detrimental, in some models of colitis. Specifically, IL-15 neutralization excaberated the pathology observed in a murine colitis model (see p. 2692; Figure 1). Furthermore, although neutralization of IL-15 reduced inflammatory infiltration and cytokine production in another colitis model, damage to the intestinal epithelium was not reduced (see abstract). The authors postulate that IL-15 may be beneficial in some instances by preventing epithelial cell apoptosis (see abstract; p. 2696, 2nd column).

Kukita *et al* (*Br. J. Haematol.*, 2002, Vol. 119, p. 467-474) teaches that adult T-cell leukemia is characterized by increased expression of both IL-15 and IL-2, and that both cytokines play a role in promoting the growth of leukemia T cells. Furthermore, neutralization of IL-15 was less effective than neutralization of IL-2 in inhibiting the growth of adult T-cell leukemia cells (see abstract; Figure 7).

Therefore, one of ordinary skill in the art would not predict that neutralization of IL-15 by the claimed method would necessarily treat all possible autoimmune diseases, or specifically, rheumatoid arthritis, inflammatory bowel disease, or leukemia. The art suggests unpredictable effects associated with IL-15 neutralization, and without further guidance from either the art or the specification, one of ordinary skill in the art would require further, undue experimentation in order to practice the claimed methods in a manner commensurate in scope with the claims.

Rejections withdrawn

2. Rejection of claim 22 under 35 USC § 112, first paragraph, regarding lack of enablement for a composition for generating neutralizing anti-IL-15 antibodies, wherein said composition comprises human IL-15 coupled to the P64k carrier protein and further comprising aluminum hydroxide, as set forth

on pages 3-4 of the prior office action mailed on 4/4/2007, is *withdrawn* in view of the fact that aluminum hydroxide is a known adjuvant for increasing antibody responses to specific antigens (see Brewer *et al, J. Immunol.* 1999, Vol. 163, pages 6448-6454).

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 14 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 14 recites a composition comprising "native IL-15". After extensive review, the Examiner is unable to find, in the Specification as originally filed, support for this newly added limitation in the claim. This newly added limitation is not expressly asserted, nor does it flow naturally from the Specification as originally filed. Claim 23 is rejected for depending from rejected claim 14.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites a composition comprising "native IL-15" as an antigen. The metes and bounds of "native" IL-15 are not defined by the claims or the instant specification in a way as to differentiate it from other types of IL-15, such as recombinant. Furthermore, in the Applicants' response to the office action mailed 9/12/2006, the Applicants stated that the specification clearly intends that the IL-15 was obtained by a process using E. coli. Claim 23 is rejected for depending from rejected claim 14.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejections maintained

1. Claim 15 *remains rejected* under 35 USC § 102(b) as being anticipated by Grabstein et al (WO 95/27722), as set forth on pages 8-9 of the office action mailed on 4/4/2007. In the response received on 8/8/2007, the Applicants set forth arguments that Grabstein et al does not anticipate the limitations of claims 14, 16, and 22 (see below), but do not present arguments as to why Grabstein *et al* would not meet the limitations of claim 15. Therefore, Grabstein *et al*, which teaches compositions of IL-15 produced in *E. coli*, wherein said compositions would be expected to generate anti-IL-15 antibodies and would have a glycosylation pattern different from autologous IL-15 by virtue of being produced in *E. coli*, meets the limitations of claim 15.

Rejections withdrawn

2. Rejection of claim 14 under 35 USC § 102(b) as being anticipated by Grabstein *et al* (US 6,013,480), as set forth on pages 6-7 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicants' amendments to the claim to recite a composition comprising IL-15 and aluminum hydroxide. The '480 patent does not teach compositions comprising IL-15 and aluminum hydroxide.

3. Rejection of claims 14, 16, and 22 under 35 USC § 102(a) as being anticipated by Grooten *et al* (US 6,344,192), as set forth on pages 7-8 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicants' amendments to the claims to recite a composition comprising IL-15 and aluminum hydroxide. The '192 patent does not teach compositions comprising IL-15 and aluminum hydroxide.

4. Rejection of claims 14, 16, and 22 under 35 USC § 102(b) as being anticipated by Grabstein *et al* (WO 95/27722), as set forth on pages 8-9 of the office action mailed on 4/4/2007, is *withdrawn* in

response to Applicants' amendments to the claims to recite a composition comprising IL-15 and aluminum hydroxide. WO 95/27722 does not teach compositions comprising IL-15 and aluminum hydroxide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections withdrawn

1. Rejection of claims 14-17, 20 and 22 under 35 USC § 103(a) as being obvious in view of the combination of Grabstein *et al* (US 6,013,480), Gonzalez *et al*, and Grabstein *et al* (WO 95/27722), as set forth on pages 9-11 of the office action mailed on 4/4/2007, is *withdrawn* in response to Applicants amendments to the claims to recite a composition comprising IL-15 and aluminum hydroxide, which is neither taught nor suggested by any of the references, and in light of the finding that the art is not enabling for methods of treating all possible autoimmune diseases by IL-15 neutralization (see above).

Rejections necessitated by amendment

2. Claims 14-15 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grabstein *et al* (WO 95/2772) in view of Gonzalez *et al* (cited in the previous office actions), and further in view of Brewer *et al* (see above).

The claims are drawn to a composition for generating neutralizing self-antibodies against autologous IL-15, wherein said composition comprises native IL-15 as an antigen and aluminum hydroxide (claim 14). The claims are further drawn to a composition for generating neutralizing self-antibodies against autologous IL-15 wherein said composition comprises recombinant IL-15 obtained in E. coli and with a glycosylation pattern different from that of autologous IL-15 (claim 15), and a composition comprising native IL-15 and aluminum hydroxide, wherein the IL-15 is coupled to a carrier protein, and specifically the P64k protein (claim 23). Finally, the claims recite a method of generating a neutralizing antibody response against IL-15 comprising administering to a host a composition comprising human IL-15 and aluminum hydroxide (claim 22).

As set forth in the previous office action, Grabstein teaches compositions of IL-15 produced in E. coli, which would inherently have a different glycosylation pattern than that of autologous IL-15, but is silent regarding compositions comprising aluminum hydroxide or IL-15 coupled to a carrier protein. Gonzalez discloses that the meningococcal protein P64k functions as an effective carrier protein when conjugated to weakly immunogenic proteins. Specifically, conjugation of P64k to other proteins induced higher antibody titers upon immunization compared to vaccination of proteins which were not conjugated to P64k. Gonzalez is silent regarding a composition comprising aluminum hydroxide. Brewer teaches that aluminum hydroxide is an adjuvant capable of inducing strong antigen-specific antibody and Th2 cytokine responses (see abstract; p. 6448, 1st column).

Therefore, one of ordinary skill in the art would be motivated to create a composition comprising IL-15 and aluminum hydroxide because the skilled artisan would know that this composition would be useful in generating antibodies useful for studying the biological actions of IL-15. The motivation to do so comes from the disclosure of Grabstein, which teaches compositions comprising IL-15, and the disclosure of Brewer, which teaches the use of aluminum hydroxide to potentiate antibody responses after vaccination. Although Grabstein does not specifically recite "native" IL-15, one of ordinary skill in the art would find it obvious to create compositions comprising aluminum hydroxide and any IL-15, recombinant or native. Furthermore, it is noted that there is no disclosed difference between the sequences of "native" and recombinant IL-15, and one of ordinary skill in the art would thus have a reasonable expectation of success in creating compositions using either native or recombinant IL-15. Finally, because Gonzalez teaches conjugation to P64k as a method of increasing the immunogenicity of proteins, a person of ordinary skill in the art would be motivated to conjugate the P64k protein to either native or recombinant IL-15 because the skilled artisan would know that such a conjugate would more effectively generate antibodies specific for IL-15. Furthermore, based on the teachings of Brewer, one of skill in the art would also be motivated to create a composition comprising an IL-15-P64k conjugate and aluminum hydroxide because the skilled artisan would know that such a composition would likely be able to generate a strong anti-IL-15 response.

Finally, because one of ordinary skill in the art would know that a composition comprising human IL-15 and aluminum hydroxide would be immunogenic when administered to a host, and claim 22 does not specify a specific host, one of ordinary skill in the art would have both the motivation and the ability to administer a composition comprising IL-15 and aluminum hydroxide to a host for the purpose of generating neutralizing antibodies against IL-15. The motivation to do comes from the teachings of Grabstein, which detail the biological activities and potential pathogenic roles of IL-15, and thus a person

of ordinary skill in the art would be motivated to create neutralizing antibodies for the study of IL-15 activities and properties.

Therefore, because the combined teachings of Grabstein, Gonzalez, and Brewer disclose the elements of the claimed compositions and provide ample motivation for creating such compositions, the subject matter of claims 14, 15, 22, and 23 is obvious in view of the cited combination.

Conclusion

No claim is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
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/Robert S. Landsman/
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